

**REMARKS**

Claims 1-3, 5-14 and 16-38 are presently under consideration. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the amendments filed February 13, 2003 have been entered in full. Claims 1-3, 5-14 and 16-38 are currently under consideration.

2-6. Applicants note that the rejection of claims 1-5, 14, 15 and 17-20 under 35 U.S.C. 112, first paragraph, has been overcome and is withdrawn.

Applicants note that the rejection of claims 14, 15, 18-20 and 24-38 under 35 U.S.C. 112, first paragraph, has been overcome and is withdrawn.

Applicants note that the rejection of claims 1-5, 14, 15, 17-20 and 24-38 under 35 U.S.C. 112, second paragraph, has been overcome and is withdrawn.

Applicants note that the rejection of claims 1-5, 14, 15, 17-20 and 24-38 under 35 U.S.C. 102(e) has been overcome and is withdrawn.

Applicants note that the rejection of claims 1-5, 14, 15, 17-20 and 24-38 under 35 U.S.C. 103(a) has been overcome and is withdrawn.

7-9. Applicants note that the Examiner has raised new grounds of rejection.

10-12. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out the claimed subject matter. Applicants traverse this rejection, and contend that the rejection is moot in light of the amended claim.

Applicants contend that one of skill in the art can readily appreciate the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended claim 5 to incorporate the Examiner's suggestion. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

13-15. Claims 1, 3, 5, 14, 17, 18, 20 and 24-38 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 5,654,168 (the “‘168 patent”) in view of U.S. Patent No. 5,639,725 (the “‘725 patent”). Applicants traverse this rejection.

MPEP 2141 outlines the basic criteria that must be considered when determining whether a reference or combination of references undermines the patentability of a claimed invention. To render a claimed invention obvious, the prior art must: (a) be considered as a whole; (b) suggest the desirability of making the combination of references required to arrive at the claimed invention; (c) not be viewed with the benefit of hindsight provided by knowledge of the claimed invention; and (d) enable one of skill in the art to arrive at Applicants’ invention with a reasonable expectation of success. MPEP 2141; *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). Applicants contend that the combination of references relied on by the Examiner fail to satisfy these criteria, and accordingly fail to render the claimed invention obvious.

The ‘168 patent fails to teach or suggest all the limitations of the pending claims. Specifically, the ‘168 patent is silent on the use of the disclosed expression system to modulate expression of angiostatin. In fact, the ‘168 patent is silent on the use of the disclosed expression system to modulate expression of any particular angiogenesis inhibitor. The Examiner has cited the ‘725 patent, directed to angiostatin nucleic acids and polypeptides, and alleges that the combination of these references is sufficient to render the claimed invention obvious. However, as a review of the factors outlined in Hodosh demonstrates, the question is not whether the Examiner can locate any two prior art references that together recite similar words as those used to describe the claimed invention. Rather, to render the claimed invention obvious, there must be some motivation to combine these two references, and that motivation cannot be supplied using hindsight obtained from examination of Applicants’ invention. Applicants contend that upon closer inspection, there is no motivation (other than the claimed invention itself) to combine the cited references. Accordingly, the combination of references fails to satisfy parts (b) and (c) of the established standard for evaluating obviousness.

The ‘168 patent provides a particular inducible expression system. The disclosed expression system may be used to modulate expression of any of a number of genes, and the ‘168 patent recites a laundry list of genes that may be so modulated. “Genes of particular interest to be expressed in cells of a subject for treatment of genetic or acquired diseases include

those encoding adenosine deaminase, Factor VIII, Factor IX, dystrophin,  $\beta$ -globin, LDL receptor, CFTR, insulin, erythropoietin, anti-angiogenesis factors, growth hormone, glucocerebrosidase,  $\beta$ -glucuronidase,  $\alpha$ -antitrypsin, phenylalanine hydroxylase, tyrosine hydroxylase, ornithine transcarbamylase, arginosuccinate synthetase, UDP-glucuronosyl transferase, apoA1, TNF, soluble TNF receptor, interleukins (e.g., IL-2), interferons (e.g.,  $\alpha$ - or  $\gamma$ -IFN) and other cytokines and growth factors.” (column 29, lines 25-35). This laundry list is the only guidance provided in the ‘168 patent to direct one of skill in the art in the selection of particular factors for use in these or other expression systems. In short, the ‘168 patent provides no such guidance. In fact, this laundry list does not even include a specific reference to angiostatin – the particular factor recited in the claimed invention. The only “guidance” provided by the ‘168 patent is the inclusion of the generic phrase “anti-angiogenesis factors” amongst the above referenced laundry list of possible factors.

The Examiner has cited the ‘725 patent to overcome the deficiencies of the ‘168 patent. However, Applicants contend that one of skill in the art would have no motivation to combine these references. The ‘168 patent provides no guidance that would lead the skilled artisan to specifically select angiostatin. In fact, the ‘168 patent does not even provide guidance that would lead one of skill in the art to select the generic class of anti-angiogenesis factors from amongst the other generic classes of factors disclosed in the application. In the absence of any suggestion to specifically select even anti-angiogenesis factors generally, one of skill in the art would have no motivation to combine the cited references to arrive at Applicants’ invention.

Given that the ‘168 patent fails to provide any motivation for selecting either anti-angiogenesis factors generally, or angiostatin specifically, for use in the disclosed expression system, Applicants contend that the only motivation for combining the cited references to arrive at Applicants’ invention is Applicants’ invention itself. The use of the claimed invention to provide motivation for combining prior art references is an example of the use of impermissible hindsight to formulate the basis of a rejection. Both the MPEP and the courts have clearly outlined that a proper rejection cannot be based on such hindsight.

Applicants contend that the ‘168 patent fails to teach or suggest all the limitations set forth in the claims. Although the ‘168 patent provides compositions and methods used for regulating gene expression, the ‘168 patent fails to teach the benefits of the particular combinations of agents set forth in the pending claims. That is, the ‘168 patent provides no

motivation to specifically select the particular elements presently claimed. MPEP 2144.08 outlines the guidelines for determining that a reference renders an invention obvious and directs the Examiner to “determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus.” Applicants contend that the ‘168 patent fails to provide motivation to select angiogenesis inhibitors from amongst the laundry list of possible factors that may be regulated using the disclosed expression system. Furthermore, the ‘168 patent fails to provide any motivation to select any particular angiogenesis inhibitors from amongst all possible angiogenesis inhibitors. Although the ‘725 patent discloses the particular angiogenesis inhibitor angiostatin, absent some motivation (other than the claimed invention) to combine the cited references, Applicants contend that the combination of references fails to satisfy the criteria necessary to render the claimed invention obvious.

Applicants contend that the claimed invention is non-obvious over the cited references. The cited references fail to satisfy the well established criteria necessary to support an obviousness rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

16. Claims 1-3, 5, 14, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the ‘168 patent and the ‘725 patent, and further in view of WO94/18317 (“Crabtree et al.”). Applicants traverse this rejection.

Applicants have discussed in detail above why the combination of the ‘168 patent and the ‘725 patent fails to render the claimed invention obvious, and WO94/18317 fails to overcome the deficiencies of the foregoing combination of references. As outlined above, the ‘168 patent provides no guidance to motivate one of skill in the art to select any one factor from amongst all possible factors that may be regulatable using the disclosed inducible system. In fact, the ‘168 patent provides nothing more than a laundry list of possible factors, and does not provide any motivation to select from amongst these factors. Accordingly, the cited references fail to satisfy the criteria necessary to render the claimed invention obvious, and Applicants respectfully request reconsideration and withdrawal of this rejection.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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**Customer No: 28120**  
Docketing Specialist  
Ropes & Gray  
One International Place  
Boston, MA 02110  
Phone: 617-951-7000  
Fax: 617-951-7050

Respectfully Submitted,



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Melissa S. Rones  
Reg. No. 54,408